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EXAMINER

HUTSON, RICHARD G

| ART UNIT | PAPER NUMBER |
|----------|--------------|
|----------|--------------|

1652

DATE MAILED: 04/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/978,297

Applicant(s)

YACOBY-ZEEVI, ORON

Examiner

Richard G Hutson

Art Unit

1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 January 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-50 is/are pending in the application.
- 4a) Of the above claim(s) 38-50 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-37 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Claims 1-50 are at issue and are present for examination.

Election/Restrictions

Applicant's election without traverse of Group I, Claims 1-37 in Paper No. 7 is acknowledged.

Claims 38-50 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Priority

Applicants statements on the first line of the specification to state that this application is a continuation-in-part of U.S. Patent Application No. 09/260,037, filed March 2, 1999, which is a continuation-in-part of U.S. Patent Application No. 09/140,888, filed August 27, 1998, which is a continuation-in-part of U.S. Patent Application No. 09/046,475, filed March 25, 1998, now U.S. Patent No. 6,153,187, issued November 28, 2000, which is a continuation-in-part of U.S. Patent Application No. 08/922,170, filed September 2, 1997, now U.S. Patent No. 5,968,822, issued October 19, 1999 and that this application further claims the benefit of priority from U.S. Provisional Patent Application No. 60/240,037, filed October 17, 2000 and the specifications of the above cited applications being incorporated by reference, is acknowledged.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper."

Specification

The disclosure is objected to because of the following informalities:

On page 3, line 6-7, applicants recite "Murry RK and Keeley FW; Biochemistry, Ch. 57 pp. 667-85". This citation is incomplete and it is suggested that applicants amend the citation to include additional information such as publisher, city and year published.

Appropriate correction is required.

Claim Objections

Claims 6, 18 and 21-37 are objected to because of the following informalities:

Claims 6 and 18 each recite "the embryo is generated in vitro via in vitro fertilization". It is suggested that this be amended to "the embryo is generated via in vitro fertilization".

Claims 21 and 31 are duplicates of claims 6 and 18, respectively.

Art Unit: 1652

Claims 21 (claims 22, 23 dependent from), 24, 25, 26 (claims 27, 28 dependent from), 29, 31 (claims 32, 33 dependent from), 34, 35, 36 and 37 each recite "IVF". It is suggested that the first time applicants refer to "in vitro fertilization", in the claims, such as in claim 6, that it be followed by "(IVF)".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-37 are directed to all possible methods of improving embryo implantation comprising contacting an embryo or a receptive uterus with an effective amount of any heparanase and implanting the embryo in a receptive uterus. The specification, however, only provides a single representative method encompassed within these claims, of improving murine embryo implantation comprising contacting a murine embryo with CHO-p65 heparanase and implanting the embryo in a receptive uterus. There is no disclosure of any particular structure to function/activity relationship in the disclosed species of heparanases used by the claimed methods, nor is there any

Art Unit: 1652

representative methods besides those for murine embryos. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yagel et al. (J. Cellular Physiology, Vol 136, pages 455-462, 1988), Nakajima et al., Heparanases and Tumor Metastasis, J. Cell Biochemistry, Vol 36, pages 157-167, 1988) and Fuks (U.S. Patent No. 5,362,641).

Yagel et al. teach that normal nonmetastatic human trophoblast cells, those cells responsible for embryo attachment to the receptive uterus, share invasive properties of malignant cells such as rapid proliferation and the ability to invade neighboring tissue including basement membrane in situ. Yagel et al. teach that inhibitors of collagenase,

Art Unit: 1652

plasmin, plasminogen and plasminogen activators completely prevented invasion of the amnion by trophoblast cell lines. Additionally treatment with mersalyl, a compound known to activate collagenase, stimulated invasion by trophoblast cell lines including under conditions in which plasmin activity was inhibited. Furthermore, Yagel et al. teach that trophoblast produce significant levels of type IV collagenase and lamin, which are both considered to be important products of metastatic tumor cells required for basement membrane invasion. Yagel et al. further teach that other models for invasiveness have been developed which show that invasive ability is related to numerous parameters such as collagenase activity, lamin production, and heparan-sulfatase (heparanase) activity.

Nakajima et al. teach that heparin sulfate degradative activities of metastatic B16 melanoma cells correlate with their lung-colonizing potential and that these HS-degrading endoglycosidases are not tumor-specific and have been found in several normal tissues and cells including the placenta.

Fuks et al. teach that the plasma membrane, extracellular matrix and basement membranes of all tissue types contain among other constituents, complex macromolecules referred to as heparan sulfate proteoglycans (HSPG). Fuks et al. teach that heparan sulfate proteoglycans have an intimate interrelationship with other macromolecules which make up the extracellular matrix, and thus their degradation may have a profound effect on the regulation of cell anchorage, movement, function and growth. Fuks et al. further teach that a number of normal physiological conditions are associated with the degradation of the extracellular matrix of various tissues, such as

neutrophil mobilization in which the cells must penetrate the endothelium of blood vessels and the underlying basal lamina in order to reach the target tissue. Fuks et al. teach the purification of heparanase obtained from human SK-HEP-1 cells and its use in formulations for therapies in which the release of FGF from the extracellular matrix would be a desirable effect such as those situations in which angiogenesis and/or the growth of fibroblasts is desired such as wound healing, ovulation, and transplantation.

One of ordinary skill in the art at the time of filing would have been motivated to use the heparanase containing formulation of Fuks et al. to treat either an embryo (trophoblast cells), a receptive uterus, or both prior to implantation of the embryo in the receptive uterus as a means of degrading the extracellular matrix associated with the uterus, and thus improving embryo implantation in the uterus. This motivation comes from the teachings of Yagel et al. who teach that the embryo trophoblast cells share many of the invasive properties of malignant cells, such as the ability to invade neighboring tissue including basement membrane, by degradation of the extracellular matrix. Yagel et al. further teach that in addition to collagenase, heparan-sulfatase (heparanase) is an important activity related to invasive ability. Nakajima et al. teach heparanase activity associated with both invasive melanoma cells as well as normal placenta. The reasonable expectation of success comes from the results of Yagel et al. who teach that an increase the activity of the enzyme collagenase, associated with trophoblast cell lines, involved in the degradation of the extracellular matrix, increased the invasiveness of the trophoblast as well as the teaching of Yagel et al. who teach that

Art Unit: 1652

in addition to an increase in collagenase activity, invasive ability is related to heparan-sulfatase (heparanase) activity.

Thus claims 1-37 are made obvious by

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

A handwritten signature in black ink, appearing to read 'Richard Hutson', with a long horizontal line extending to the right.

Richard Hutson, Ph.D.
Patent Examiner
Art Unit 1652
April 4, 2003